

**“EXERCISE TOLERANCE AND POST EXERCISE DIASTOLIC
FILLING PATTERN IN PATIENTS WITH RESTING GRADE I
DIASTOLIC DYSFUNCTION ”**

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CERTIFICATE

This is to certify that **Dr. SARAVANABABU.S**, Post graduate student [2010-2013] in the Department of Cardiology, Government General Hospital, Chennai & Madras Medical College, Chennai-600003, has done this Dissertation on “**EXERCISE TOLERANCE AND POST EXERCISE DIASTOLIC FILLING PATTERN IN PATIENTS WITH RESTING GRADE I DIASTOLIC DYSFUNCTION**” under my guidance and supervision in partial fulfillment of the regulations laid down by The Tamil Nadu Dr. M.G.R Medical University, Chennai, for DM Cardiology –Branch II examination to be held in August, 2013.

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DECLARATION

I hereby solemnly declare that the dissertation titled **“EXERCISE TOLERANCE AND POST EXERCISE DIASTOLIC FILLING PATTERN IN PATIENTS WITH RESTING GRADE I DIASTOLIC DYSFUNCTION”** was done by me at Department of Cardiology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during 2012 under the guidance and supervision of my unit Chief Prof. Dr.V.E.DHANDAPANI, MD,DM.

The dissertation is submitted to the Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of requirement for the award of D.M. (Branch-2) in Cardiology.

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ABBREVIATIONS

PROFORMA

MASTER CHART

CONSENT FORM

ETHICAL COMMITTEE APPROVAL LETTER

ANTIPLAGIARISM CERTIFICATE

INTRODUCTION

Diastolic dysfunction is one of the commonly seen abnormalities in heart disease patients. It is commonly associated with diabetes, hypertension, LV hypertrophy, increasing age and coronary artery disease. These type of abnormalities are seen even in patients with normal systolic function.

Patients having normal LV systolic function increase their cardiac output during exercise by increasing their stroke volume and heart rate. Initially stroke volume increases and later increase in heart rate is responsible for additional increase in cardiac output.

Grade I DD, although a common abnormality, is often not given much importance in the assessment of cardiac function. In subjects with resting grade 1 DD, exercise tolerance may be normal or reduced.

To predict the exercise tolerance various parameters are used. The promising parameters among them are E/e' ratio and exercise transmitral Doppler parameters which predicted exercise tolerance.

To maintain filling volume in patients with normal systolic function and resting Grade I DD, atrial compensation has already occurred. On exercise it is not very much clear whether increase in

cardiac output occurred due only to increase in heart rate or increase in stroke volume also is responsible for increase in cardiac output in patients with resting Grade I DD.

All subjects with Grade I DD are not similar with respect to their functional capacity. Hence this study intends to categorize the subset of subjects with Grade I DD having reduced exercise tolerance. This categorization may help in the management strategy when dealing with diastolic dysfunction.

AIMS AND OBJECTIVES

1. To assess the functional capacity/exercise tolerance of patients with resting Grade I DD.
2. To identify different patterns of Doppler parameters before and after exercise in patients with resting Grade I DD.
3. To assess the association between LV filling pattern post exercise and functional capacity/exercise tolerance in patients with resting Grade I DD.
4. To identify the subgroup of patients with grade I DD who show increase in LV filling pressures after exercise.

REVIEW OF LITERATURE

Definition of Diastolic function

Normal ventricular diastolic function is the ability of the ventricles to relax after ejection and to allow adequate filling to a normal end-diastolic volume during rest and exercise without abnormal increase in LV diastolic pressure and left atrial pressure.

Definition of diastolic Dysfunction

It is defined as the impaired capacity of the ventricles to accept blood to fill without a compensatory increase of atrial pressure.

PHYSIOLOGY OF DIASTOLE

Diastole is the cardiac cycle phase during which the ventricles are relaxed and the blood is flowing from right and left atrium to the right and left ventricles respectively. The left atrium receives blood from the lungs through the pulmonary veins. The blood flows from atria to ventricles through atrioventricular valves (mitral at the left and tricuspid at the right). Diastole is divided into four phases as isovolumetric relaxation, a rapid filling phase, a slow filling phase and atrial systole. Ventricles are first filled by the pressure gradient and at the end it is by

the atrial contraction. Isovolumetric relaxation phase is the time between aortic valve closure and mitral valve opening during which ventricular pressure decreases without significant change in volume. During this phase ventricular pressure falls from peak which is attained at the end of systole. This phase is energy dependent and may be more susceptible to ischemia. In rapid filling phase most of the ventricular filling occurs which is partially energy dependent. When ventricular pressure falls below the atrial pressure, atrioventricular valves open and the blood flows from atria to ventricles. As this phase progresses further increase in ventricular volume is affected by the factors affecting stiffness of the myocardium. During slow filling phase as the ventricles continue to fill with blood, the intraventricular pressure begins to rise as the ventricles become less compliant. This reduces the pressure gradient across the AV valves which causes decrease in the ventricular filling. This phase is also affected by the above said factors. Passive stiffness will be increased by fibrosis resulting from ischemia, infarction or infiltrating process, myocyte hypertrophy resulting from poorly controlled hypertension, valvular heart diseases. About 90% of the ventricular filling occurs at the end of this phase. The atrial systolic phase contributes to about 10% of ventricular filling but in certain diseased states it may even contribute to about 40% (in patients with diminished early relaxation).

DETERMINANTS OF DIASTOLIC FUNCTION

Factors that determine DD are relaxation of the myocardium, load (preload, afterload), dys-synchrony of myocardial function, myocardial stiffness, chamber geometry and wall thickness.

Relaxation of the myocardium

It is an energy dependent process by which myocardium returns to its unstressed length and force. It comprises of iso-volumic relaxation and rapid filling period. It is affected by load, inactivation of the contractile proteins and dyssynchrony of myocardial function.

Load

It includes preload and afterload. Magnitude, duration and timing in the cardiac cycle determine the effect of load on relaxation of myocardium.

Inactivation of contractile proteins

It is an energy dependent process in which the actin and myosin filaments detach from each other due to expulsion of calcium from the cytosol.

Dyssynchrony of myocardial function

Minimal degrees of dyssynchrony exist even in normal myocardium. Diastolic dysfunction occurs as a result of exaggeration of this dyssynchrony.

Myocardial stiffness

It is the stiffness due to the elastic force offered by the cytoskeleton including microtubules, titin, desmin, actin, actinin, myomysin. Extrinsic factors like extracellular matrix also play a role.

Wall thickness

Myocyte hypertrophy and increase in extracellular matrix cause LVH leading to increase in the myocardial stiffness. Increase in the ratio of LV mass to LV volume causes structural remodelling leading to diastolic heart failure whereas increase in the ratio of LV volume to LV mass causes systolic heart failure.

Chamber Geometry

Shape and size of the LV cavity is also a determinant of diastolic function. Increase in dimensions and volume of the LV causes increase in chamber stiffness.

Other Extrinsic factors determining diastolic function

Structures like right ventricle, left atrium, pulmonary vein, mitral valve and pericardium also determine the diastolic function of LV. Increase in heart rate affects the diastolic function by decreasing the diastolic filling time and increasing the oxygen demand. This leads to decrease in coronary perfusion time.

EVALUATION OF DIASTOLIC FUNCTION

Echocardiography, radio-nuclide studies, MRI and invasive studies are used for assessing diastolic function.

Echocardiographic assessment of diastolic function:

Echocardiography is simple ,cheaper and widely available (can be done even at bedside). It can be repeated any number of times for reassessment.

A comprehensive study of 2D echo (volume, EF,LV mass, severity of mitral regurgitation), flow Doppler echo (mitral flow velocity, pulmonary venous flow velocity, colour Doppler, M-mode study of flow in LV cavity and tissue Doppler echo (annular velocities, strain rate imaging) offers adequate data for assessment of diastolic dysfunction.

ECHO-DOPPLER PARAMETERS OF DIASTOLIC FUNCTION

IVRT

Early diastolic left ventricular relaxation can be studied by measuring IVRT. IVRT increases when there is prolonged relaxation of left ventricle. On the other hand when there is elevated pressure of left atrium, IVRT is shortened. IVRT is measured using pulse wave Doppler from a modified apical four chamber view. Gain and filters are adjusted so that aortic closure and mitral opening are clearly visualized. Measurements are taken at end expiration and a faster sweep speed is used. Rate of relaxation of myocardium is thus indicated by IVRT. But IVRT measurements has a significant limitation in the sense that IVRT is influenced by numerous factors. Few such factors are age, heart rate, systolic function, left atrial pressures etc. This results in the non specific nature of IVRT. So IVRT should not be used in isolation for diastolic dysfunction assessment.

MITRAL INFLOW PARAMETERS

One of the most important parameters for assessing diastolic function is an accurate measurement of mitral inflow velocity. This is based on the factor that velocity curve reflects instantaneous pressure

gradient between left atrium and left ventricle at any point of cardiac cycle.

Mitral inflow recordings are done from apical four chamber view. Sample volume is placed at the tip of mitral leaflets. Sample volume size should be about 2mm. Spectral gain and filter settings should be adjusted to get a clean envelop so that accurate time of beginning and end of mitral inflow is obtained.

The important parameters to be measured in mitral inflow are :

- 'E' wave - peak early filling velocity
- 'A' wave - peak filling velocity during atrial systole
- E/A ratio
- Deceleration time of the early filling velocity

Deceleration time is the time between early peak inflow velocity ('E'- wave) to the end of rapid early filling phase. Deceleration time and chamber stiffness are inversely related. Various factors can influence the mitral inflow patterns including sinus tachycardia, first degree AV block, atrial fibrillation and mitral valve diseases. Mitral doppler parameters are also affected by age, gender, heart rate, bundle branch block and RV over load states.

COLOUR M-MODE FLOW PROPAGATION VELOCITY(V_p)

During diastole blood flow increases from mitral valve orifice towards LV apex. Propagation velocity can be measured throughout diastolic period with colour Doppler M-mode.

The slope of the early diastolic wave top apex contour is the most often used parameter. Factors which affects this measurement include ventricular geometry, chamber volume, wall motion abnormalities and systolic function. Hence, propagation velocity should not be used in isolation. It is mainly used in patients with LV dilatation with decrease systolic function.

TISSUE DOPPLER METHODS

Tissue Doppler records low velocity high amplitude signals arising from movement of the myocardium. As a result of myocardial segment shortening and lengthening causing mitral annulus to move longitudinally towards or away from the relatively fixed LV apex during systole and diastole respectively. From the four chamber view, the sample volume is placed in the annulus where mitral valve is getting inserted. Both septal (medial) and lateral sides to be recorded. Spectral gain to be lowered so as to ensure a crisp and reproducible tracing. The sweep speed

recommended is between 50 and 100 cm/sec. Tracing to be obtained in three or more consecutive cycle at end expiration.

One of the most useful parameters to be measured in tissue Doppler is the peak annular velocity in early diastole (e'). e' velocity chiefly depends on relaxation of left ventricle. e' is not load dependent and e' is usually incorporated in the E wave velocity and an important ratio E/e' is obtained. The main use of E/e' ratio is that it indicates filling pressures in the setting of abnormal diastolic function. One of the major limitations of E/e' ratio is that the two values are obtained in two different cardiac cycles.

Pulmonary venous flow patterns

Pulmonary venous flow velocities are recorded at the place where pulmonary veins join the left atrium. Apical 4 chamber view is used for this recording.

It comprises of 3 major components

1. Antegrade systolic wave(2 peaks S1&S2)
2. Diastolic wave(D)
3. Retrograde wave corresponding to atrial systole(Ar)

Commonly reported parameter is S/D ratio. Ar-A correlates with LVEDP

To summarize the various echocardiographic tools for diastolic assessment are as follows:

1. M- mode measurement
2. 2-D ECHO measurement
3. Doppler measurement – Transmitral Doppler measurement
Pulmonary venous flow measurement
4. Colour M-mode
5. Tissue Doppler imaging methods

Types of Diastolic filling patterns in DD:

Many parameters are used to grade the diastolic filling pattern^{1,2}.

The various patterns of diastolic function observed are:

1. Normal pattern
2. Grade 1 DD
3. Grade 2 DD (pseudonormalization)
4. Grade 3 DD (reversible filling pattern)
5. Grade 4 DD (irreversible filling pattern)

Normal diastolic filling pattern:

Normally in persons not having diastolic dysfunction, E wave is greater than A wave resulting in E/A ratio > 1.5 . The deceleration time

(DT) is 160 – 240 msec. E/E' ratio is < 8 . As age advances E velocity and A velocity almost becomes similar.

Grade 1 DD:

This is a mild form of DD and is an early abnormality of diastolic function. Various names are given to describe this form of DD like impaired relaxation pattern, delayed relaxation pattern, reversed E/A pattern. In subjects with Grade 1 DD filling pressures are normal. They have E/A ratio less than 1. Deceleration time of > 240 milliseconds.

Cardiac conditions that cause this type of DD are LVH, myocardial ischemia, myocardial infarction, hypertrophic cardiomyopathy and diabetes mellitus. These patients have increase in the IVRT. Other ECHO abnormalities noted in patients with DD are septal $e' < 7$ cm, mitral flow propagation velocity < 50 cm/sec and $E/e' \geq 8$.

A subgroup of patients with Grade I DD have an unique echo abnormality. They have E/A ratio < 1 but $E/e' > 15$ indicating increase in filling pressure which is not usually seen in patients with grade 1 DD. This abnormality is designated as grade 1a DD.

Grade 2 DD:

This is a moderate form of DD. This stage of DD is also called pseudonormalization of DD. The echo parameters resemble the normal diastolic filling pattern such as E/A ratio between 1 to 1.5 and DT ranging 160 to 200 milliseconds. The following features are used to differentiate the pseudonormalization of DD from normal filling pattern of diastolic function:

1. $e' < 7$
2. presence of mid diastolic flow
3. With valsalva maneuver the underlying impaired relaxation pattern is unmasked whereby E/A ratio decreases by > 0.5 .
4. With valsalva maneuver if A velocity increases – it indicates pseudonormalization of diastolic function.
5. Shortening of mitral A duration and prolongation of pulmonary vein atrial flow reversal which exceeds mitral A duration indicating pseudonormalization.

Grade 3&4 diastolic dysfunction

These are the severe forms of diastolic dysfunction. Grade 3 diastolic dysfunction is the reversible pattern of diastolic dysfunction.

Grade 4 diastolic dysfunction is the irreversible pattern of diastolic dysfunction. These type of diastolic dysfunctions are also termed as restrictive filling pattern or restrictive physiology. Examples of cardiac abnormalities which cause this severe type of restrictive diastolic dysfunction pattern are constrictive pericarditis, advanced restrictive cardiomyopathy , severe coronary artery disease, decompensated systolic heart failure, advanced restrictive cardiomyopathy, severe coronary artery disease and acute severe aortic regurgitation.

Shortened deceleration time is seen in grade 3 & 4 diastolic dysfunction. In these abnormalities less compliant ventricle receiving blood in the early rapid diastolic filling phase causes rapid equalization of pressures between LV and LA resulting in shortened of deceleration time. Eventhough atrial contraction causes an increasing in LA pressure 'A' velocity and duration are decreased since LV pressure rises more rapidly than that of LA pressure.

Hence the echocardiographic abnormalities that are noted in restrictive filling with severe diastolic dysfunction are:

1. Increased 'E' velocity
2. Decreased 'A' velocity (markedly reduced than 'E')
3. E/A ratio >2

4. Decreased DT (<160 milli seconds)
5. IVRT (<70 milli seconds)
6. Pulmonary vein systolic forward flow velocity is reduced
7. Mitral annulus velocity (Ea) is decreased
8. E/e ' ratio is more than 15.
9. In grade 3 diastolic dysfunction (reversible form of severe diastolic dysfunction) with performance of valsalva maneuver the restrictive filling pattern may be restored to grade 1 to 2 pattern.

Clinical applications of diastolic function assessment

The following clinical scenarios warrant the assessment of diastolic function and should form an essential part during the echocardiographic assessment in these clinical scenarios

1. Filling pressure assessment during rest and with exercise. In patients with reduced LV systolic function, E/A ratio of 1.5 or more and deceleration time of 140 or more indicates increase in LV filling pressure. But in the presence of normal LVEF and diastolic heart failure these parameters do not have a reasonable correlation with filling pressures.

One of the best echocardiographic parameters to assess the filling pressures at all degrees of LVEF is E/e' ratio. There is a good correlation between PCWP and E/e' ratio^{1,2}. If E/e' ratio is more than or equal to 15,

PCWP is 20mm Hg. E/e' ratio assessment after exercise is done to assess filling pressures^{3,4}. If E/e' is less than 8, PCWP is usually within normal limits.

2. Clinical assessment of cardiomyopathy^{5,6}, constrictive pericarditis^{7,8} and diastolic heart failure:

Since LVEF is normal in these cardiac conditions, assessment of diastolic function helps in diagnosing these conditions before they manifest clinically.

3. Prognostic assessment

Various echocardiographic diastolic parameters are found to have powerful prognostic implications in various cardiac conditions. They are E velocity, E/A ratio, DT, E/e' & LA volume^{9,10}.

STRESS ECHOCARDIOGRAM:

Stress uses the ultrasound imaging of the heart to assess the wall motion in response to the physical stress. It assesses how the heart is pumping to meet the needs of the body. It is a non-invasive test.

TYPES OF STRESS ECHOCARDIOGRAPHY:

- 1.Exercise stress echo (using treadmill or bicycle)
2. Phamacologic stress echo(mainly using dobutamine)

INDICATIONS:

- -for diagnosis of coronary artery disease
- -to estimate the severity of coronary artery disease
- to assess pulmonary artery systolic pressure in pulmonary hypertension.
- to assess severity of valvular heart disease like mitral stenosis,mitral regurgitation.
- in the suspicion of cardiac disease in case of dyspnea

PROCEDURE:

To assess the basic wall motion of the heart, imaging of the heart is done at rest. Then the patient is asked to walk on treadmill or to do other exercise modality or by using a pharmacological agent to achieve target heart rate or 80%of the age predicted maximum heart rate. Blood pressure and electrocardiogram are monitored throughout the procedure. Food and drink should not be taken three hours prior to the procedure.

INTERPRETATION:

Interpretation is qualitative. Normal response is augmentation in all areas. It assesses the wall motion abnormality which indirectly indicates the ischemia of the coronary arteries (coronary artery disease). It assesses the ventricular systolic function of the heart. Direct imaging of the arteries not assessed by the stress echo. It is assessed only by the cardiac catheterisation.

If there is an abnormal result, there may be need for coronary angiography, angioplasty and stent placement, changes in medicines, bypass surgery etc.

CONTRAINDICATIONS:

- Stress echo is not done within 24 hours of troponin positive acute coronary syndrome and within 7 days after STEMI.
- Recent history of life threatening arrhythmia
- recent pulmonary embolism or infarction
- left ventricular failure with symptoms at severe fixed left ventricular outflow tract obstruction.
- -blood pressure more than 220/120
- -severe hyperkalemia

- -acute endocarditis, pericarditis, myocarditis, deep vein thrombosis, thrombophlebitis.
- -in bronchospasm, BP<90mmHg, 2nd or 3rd degree heart block and sick sinus without pacemaker in dobutamine stress test.

COMPLICATIONS:

The incidence of complications is very low with stress echocardiography

Rarely complications like abnormal heart rhythm, fainting and myocardial infarction may occur

ACCURACY:

For exercise stress echo: Sensitivity - 74% - 97% & Specificity - 64%-86%

For dobutamine stress echo: Sensitivity -61 % -95 % & Specificity - 51 %-95 %

LIMITATIONS:

Sensitivity of detecting multivessel disease in normal ventricles is only 50% but it is readily detected in the presence of infarction. In single vessel disease if the involved vessel is small or distal sensitivity is low since there is only mild limitation of flow.

STUDY DESIGN AND METHODOLOGY

Setting

Outpatient sections of the Department of Cardiology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai – 3.

Study design

Single centre, case control analytical study

Period of the study

The study was done between January 2012 to December 2012

Ethical Committee Approval

Approval was obtained from the Institutional Ethical Committee.

Inclusion criteria

Group I

Subjects with resting grade I DD (E/A ratio less than 1 and DT less than 240 msec) in sinus rhythm with normal resting wall motion and ejection fraction more than 55%.

Group II

Subjects with normal resting diastolic function (E/A ratio > 1) in sinus rhythm with normal resting wall motion and ejection fraction more than 55%.

Exclusion Criteria

- Age less than 30 years and more than 60 years
- Valvular regurgitant lesions of moderate and severe grades
- Coronary artery disease
- Chronic diseases like chronic kidney disease, chronic liver and lung diseases
- Pregnancy
- Subjects with arrhythmias
- Subjects with systolic dysfunction (EF $< 55\%$)
- Uncontrolled Hypertension (SBP > 200 mm Hg, DBP > 110 mm Hg)
- Acute systemic illnesses like pulmonary embolism, aortic dissection
- Subjects with inability to perform treadmill test

Sample size

212 consecutive patients visiting the outpatient section of the cardiology department were screened, of which 108 patients were excluded from the study. The remaining 104 patients were recruited for the study after applying the inclusion criteria.

Consent

An informed written consent was obtained from the participants of the study.

Selection of study subjects

Out of the 212 consecutive patients presenting to the outpatient section of Department of Cardiology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, 108 patients were excluded from the study after applying the exclusion criteria. The remaining 104 subjects were included in the study after applying the inclusion criteria. Based on the presence of resting Grade I DD, the study subjects were divided into two groups namely resting Grade I DD group (Group I) and resting normal DD group (Group II). Comparison was made between the characteristics of the two groups.

Details collected from the study subjects

Age of the study subjects ranged from **32 to 57 years**. Detailed history of the clinical symptoms, associated conditions like diabetes, systemic hypertension were recorded in the study proforma.

Laboratory data of the study subjects include Fasting blood sugar, 2 hrs post glucose blood sugar/Random blood sugar, serum urea , serum creatinine.

METHODOLOGY

Resting Echocardiography

Resting and exercise echocardiography were done using ESOATE echocardiograph. Echo images were acquired before and after symptom limited treadmill exercise with patient in left lateral position. Care was taken to set gain and filter settings so that quality of the trace is optimal and spectral broadening is minimized. Images were recorded in digital format and analysis was done offline. Views obtained include parasternal, apical four chamber five chamber and subcostal views. Color Doppler, continuous wave doppler and pulse wave doppler data across each valve were obtained. Trans-mitral and trans-aortic Doppler data were obtained. Resting transmitral Doppler was done with a sample volume of 5X5 mm

just beyond the mitral leaflet tips. Sweep speed used was 100 mm/sec. Transaortic Doppler was done using apical five chamber view with sample volume of 5x5 mm just beyond the aortic leaflets with a sweep speed of 100 mm/sec.

Exercise stress testing

Exercise stress testing was performed using Schiller Treadmill. Standard Bruce Protocol was used for this study. Subjects were instructed to discontinue medications like beta blockers on the day of treadmill exercise testing. The subjects when performing the treadmill exercise were accompanied by a physician who encouraged the subjects for performing maximal exercise. Subjects were asked to terminate the exercise when symptoms of fatigue, chest pain, shortness of breath develop.

Post Exercise Echocardiography

Post-exercise subjects were asked to lie down within 45 to 60 seconds and was done in the parasternal long axis, apical four chamber, five chamber and subcostal views. During transmitral Doppler post-exercise the subjects were asked to hold the breath in expiration within 2 minutes post-exercise to make the E and A waves distinctly seen.

Demographic variables

Incidences of DM, LVH, SHT were compared in both groups.

Hypertension

Subjects with known history of hypertension or BP > 140/90 mm Hg were considered for the study as hypertensives.

Diabetes

Subjects with known past history of diabetes or fasting blood sugar >126 mg/dl or 2 hours post glucose blood sugar >140 mg/dl or random blood sugar >200 mg/dl with symptoms of diabetes were considered for the study as diabetics

LVH

Subjects with LV mass index more than 96 grams/ m² among women and more than 115 grams / m² were considered as having LVH.

Exercise stress test variables

HR, SBP, DBP at rest were obtained. Peak HR, SBP, DBP were obtained.

LV volumes and masses

LVEDV and LVESV were obtained at rest and postexercise using biplane Simpson's method. LV mass at rest was calculated from 2 D Echo data as per the recommendations of American Society Echocardiography.

Doppler variables

Three consecutive cardiac cycles were obtained and their average was used for all calculations. Using transmitral Doppler indices peak rapid filling velocity(E) and peak atrial filling velocity(A) were obtained. Deceleration time(DT) was measured as the time interval between peak rapid filling velocity and the time when mitral flow decelerated to baseline. Diastolic filling period was measured as the interval between the starting and the end of transmitral spectral tracing. IVRT was measured as the time interval between aortic velocity spectrum and the onset of mitral velocity spectrum.

Conflict of interest

There is no conflict of interest in this study

Financial Support

This work was not supported by any grant from any funding authority or charitable organisation.

Statistical Analysis

Discrete variables in this study included sex, diabetes, hypertension, LVH. Continuous variables in this study include age, heart rate, systolic BP, diastolicBP, E-velocity, Avelocity, IVRT, DT, RFP, AFP, E/e'. Continuous variables were described as mean \pm standard deviation. For comparison between discrete variables Chi square test was used. For comparing discrete with continuous variables Student 't' test was used. Data was analyzed by SPSS statistical software and P value of <0.05 was considered significant and P value of <0.01 was taken as more significant.

OBSERVATION AND RESULTS

Group I in the study indicates subjects with resting Grade I DD.

Group II in the study indicates subjects without resting Grade I DD.

Table 1: Characteristics of the study subjects

Characteristics	Group I Number (Percentage)	Group II	P value
Age (years)	49.3 ± 5.9	47.6 ± 6.9	0.18
Male	35(67.3)	40(76.9)	0.27
Female	17(32.7)	12(23.1)	0.27
Diabetes mellitus	23(44.2)	0(0)	<0.001
Systemic Hypertension	32(61.5)	0(0)	<0.001
Left ventricular hypertrophy	31(59.6)	0(0)	<0.001

Characteristics of the 104 participants of the study group are given in table 1.

The mean age in group I was 49.3 ± 5.9 and in group II was 47.6 ± 6.9 . They are age matched. In the study, number of males were

35(67.3%) and 40(76.9%) in group I and group II respectively. Likewise, number of females were 17(32.7%) and 12(23.1%) in the first and second groups. The study population was also sex matched.

Diabetes mellitus comprised 23 subjects(44.2%) in the group I whereas systemic hypertension subjects were 32(61.5%) . The subjects who had left ventricular hypertrophy were 31(59.6%).

In Group II none of the subjects had diabetes mellitus, systemic hypertension and left ventricular hypertrophy.

So, in this study, the subjects were not only properly age matched but also sex matched apart from the group I having more subjects with systemic hypertension, diabetes mellitus and left ventricular hypertrophy.

Table 2: Characteristics of the study subjects in resting state

Characteristics	Group I Mean \pm SD	Group II Mean \pm SD	P value
Resting Heart rate (per minute)	76.8 \pm 5.3	75.7 \pm 5.1	0.27
Resting SBP (mm Hg)	126.4 \pm 8.8	118.3 \pm 6.09	<0.001**
Resting DBP (mm Hg)	81.3 \pm 5.1	71.0 \pm 3.0	<0.001**
Ejection fraction (%)	61.6 \pm 4.3	61.1 \pm 4.6	0.52
E/A	0.74 \pm 0.03	1.35 \pm 0.02	<0.001**
Deceleration Time (milli seconds)	263.7 \pm 16.8	190.9 \pm 11.7	<0.001**

** - Significant (P value < 0.001)

Age-wise distribution of the study group is given in table 2.

Among Group I subjects the age range was 35 years to 57 years. Among

Resting heart rates were around 77 in group I and 76 in group II.

Resting systolic blood pressure(mm Hg) were 126.4 \pm 8.8 and 118.3 \pm

6.09 in group I and group II. Resting diastolic blood pressure (mm Hg) were 81.3 ± 5.1 and 71.0 ± 3.0 in group I and group II respectively. Both systolic and diastolic blood pressure showed statistical significance between the two groups at resting stage itself inferring that the group II Subjects were normotensives.

In the study population left ventricular ejection were normal in both the groups. A decrease in left ventricular ejection fraction may by itself will cause dyspnoea and would interfere with diastolic parameters.

Most importantly, E/A reversal was showing a significant statistical correlation at rest between the two groups inferring that the group II Subjects having normal diastolic filling pattern.

As expected, deceleration time(ms) was prolonged(263.7 ± 16.8) in th group I subjects and was within normal limits in the group II Subjects (190.9 ± 11.7) thereby resulting in significant statistical correlation between the two groups.

Significant statistical difference was noted between the study groups with respect to resting SBP, resting DBP, E/A ratio and deceleration time. There was no statistical significant differences in age, resting heart rate and ejection fraction.

Table 3 shows heart rate increased from 76.8 ± 5.3 at rest to 148.1 ± 12.6 exercise. This showed statistical significance.

There was also a statistical significant correlation between systolic blood pressure and diastolic blood pressure with regard to rest and exercise. Even then the correlation between systolic blood pressure requires special emphasis as this was very much significant statistically. (Fig. 1 & Fig. 2).

The E velocity showed an increase from 64.25 ± 11.8 to 76.2 ± 9.8 and the increase was statistically significant whereas A velocity showed an increase but it was not statistically significant. The implication from this observation is E rise is more than A rise which is reflected in E/A ratio change from rest to exercise. E/A ratio increased from to at rest and exercise. (Fig. 3 & Fig. 4).

**Table 3: Changes with exercise in subjects with resting
Grade I DD (Group I)**

Doppler variables	Rest Mean \pm SD	Exercise Mean \pm SD	P value
Heart rate (beats /min)	76.8 \pm 5.3	148.1 \pm 12.6	<0.001**
SBP (mm Hg)	126.4 \pm 8.8	148.7 \pm 10.8	<0.001**
DBP (mm Hg)	81.3 \pm 5.1	78.65 \pm 7.5	0.045*
E (cm/sec)	64.25 \pm 11.8	76.2 \pm 9.8	<0.001**
A (cm/sec)	86.3 \pm 13.2	87.7 \pm 4.26	0.463
E/A	0.74 \pm 0.03	0.87 \pm 0.13	<0.001**
IVRT (millisec)	87.23 \pm 21.2	68.0 \pm 24.5	<0.001**
DT (millisec)	263.7 \pm 16.8	262.1 \pm 20.7	0.636
RFP (millisec)	200.1 \pm 29.7	159.3 \pm 21.5	<0.001**
AFP (millisec)	151.6 \pm 17.5	127.8 \pm 13.5	<0.001**
E/e'	9.05 \pm 0.35	10.6 \pm 1.9	<0.001**

** - very significant, * significant

IVRT showed a decrease from 87.23 ± 21.2 to 68.0 ± 24.5 at rest and exercise which was showing statistical significance inferring that despite the patient having grade I diastolic dysfunction at rest did not show an increase in IVRT. (Fig. 5 & Fig. 6).

Deceleration time did not show statistical significance both during rest and exercise. The observation from this finding is the diastolic dysfunction did not deteriorate further after exercise further implicating that majority of the subjects were not in severe diastolic dysfunction. (Fig. 5 & Fig. 6).

Rapid filling period and atrial filling period showed a decline post exercise and they also showed statistical significance.

E/e' ratio showed an elevation from 9.05 ± 0.35 to 10.6 ± 1.9 and this was statistically significant. From the above observations, there is a decline in diastolic function after exercise in subjects with pre-existing diastolic dysfunction but the decline of diastolic dysfunction did not result in a major change in deceleration time whereas IVRT showed a decline. IVRT, E/e' are important parameters in assessing of diastolic function when compared to deceleration time.

Table 4: Changes with exercise in subjects without resting**Grade I DD (Group II)**

Doppler variables	Rest Mean \pm SD	Exercise Mean \pm SD	P value
Heart rate (beats /min)	75.7 \pm 5.1	164.1 \pm 6.7	<0.001**
SBP (mm Hg)	118.3 \pm 6.1	156.7 \pm 4.6	<0.001**
DBP (mm Hg)	71.1 \pm 3	69.6 \pm 2.9	0.017*
E (cm/sec)	73.4 \pm 7.6	94.2 \pm 9.4	<0.001**
A (cm/sec)	54.1 \pm 5	86.6 \pm 11.3	<0.001**
E/A	1.35 \pm 0.02	1.09 \pm 0.04	<0.001**
IVRT (millisec)	68.9 \pm 9.9	28.2 \pm 12.6	<0.001**
DT (millisec)	190.9 \pm 11.8	209.7 \pm 14.9	<0.001**
RFP (millisec)	233.6 \pm 19.4	173.9 \pm 25.6	<0.001**
AFP (millisec)	107.8 \pm 16.9	104.7 \pm 10.7	0.235
E/e'	7.04 \pm 0.5	7.34 \pm 0.43	0.02*

** - very significant, * significant

A similar comparison was done in group II subjects (Table 4). Interestingly all parameters showed statistical significance.

There was an increase in heart rate from resting to exercise. At the same time there was an increase in systolic blood pressure from rest to exercise which correlated significantly and there was a decline in diastolic blood pressure from rest to exercise.

Both E and A velocity showed an increase but the increase of A was significantly higher than that of E. Hence there is a decrease in E/A ratio from at rest to at exercise.

IVRT showed a marked decline from rest to exercise and DT showed an increase from rest to exercise. These are expected findings in normal subjects.

Duration of rapid filling period reduced from 233.6 ± 19.4 to 173.9 ± 25.6 which is statistically significant. On the contrary duration of atrial filling period showed only a modest decrease from 107.8 ± 16.9 to 104.7 ± 10.7 which is not statistically significant.

E/e' showed an increase from 7.04 ± 0.5 to 7.34 ± 0.43 which is statistically significant.

So, from these findings in these subjects who had normal diastolic function at rest are similar to the group I subjects with regard to heart rate, systolic blood pressure, diastolic blood pressure, E velocity, A velocity. But there is an important difference with reference to E/A ratio.i.e., E velocity showed a greater increase in group I subjects whereas A velocity showed a greater increase in group II subjects after exercise.

The most important inference from this finding is that in group I subjects E/A ratio increased whereas E/A ratio decreased in group II subjects.

**Table 5: Comparison between resting Doppler variables Of
Group I and Group II**

Doppler variables	Group I Mean \pm SD	Group II Mean \pm SD	P value
Heart rate (beats /min)	76.8 \pm 5.3	75.7 \pm 5.1	0.274
SBP (mm Hg)	126.4 \pm 8.8	118.3 \pm 6.1	<0.001**
DBP (mm Hg)	81.3 \pm 5.1	71.1 \pm 3	<0.001**
E (cm/sec)	64.25 \pm 11.8	73.4 \pm 7.6	<0.001**
A (cm/sec)	86.3 \pm 13.2	54.1 \pm 5	<0.001**
E/A	0.74 \pm 0.03	1.35 \pm 0.02	<0.001**
IVRT (msec)	87.23 \pm 21.2	68.9 \pm 9.9	<0.001**
DT (msec)	263.7 \pm 16.8	190.9 \pm 11.8	<0.001**
RFP (msec)	200.1 \pm 29.7	233.6 \pm 19.4	<0.001**
AFP (metre sec)	151.6 \pm 17.5	107.8 \pm 16.9	<0.001**
E/e'	9.05 \pm 0.35	7.04 \pm 0.5	<0.001**

** very significant

Table 5 shows resting parameters of group I and group II. The heart rate is similar in both groups. There is a significant difference between systolic blood pressure in group I and group II, inferring that group I constituted more hypertensive patients.

Similarly due to the presence of more hypertensives in group I, diastolic blood pressure showed an increase in the group I subjects than group II subjects.

E velocity is decreased and A velocity is increased in group I subjects due to atrial contribution occurring in the grade I diastolic group. Due to the same fact E/A ratio is reduced in group I.

IVRT and DT are prolonged in group I subjects than group II indicating the presence of mild diastolic dysfunction in this group.

Rapid filling period and atrial filling period are increased in group I subjects and E/e' is also increased in this group which is indicative of high filling pressures when compared to group II.

**Table 6: Comparison between post exercise Doppler variables
of Group I and Group II**

Doppler variables	Group I Mean \pm SD	Group II Mean \pm SD	P value
Heart rate (beats /min)	148.1 \pm 12.6	164.1 \pm 6.7	<0.001**
SBP (mm Hg)	148.7 \pm 10.8	156.7 \pm 4.6	<0.001**
DBP (mm Hg)	78.65 \pm 7.5	69.6 \pm 2.9	<0.001**
E (cm/sec)	76.2 \pm 9.8	94.2 \pm 9.4	<0.001**
A (cm/sec)	87.7 \pm 4.26	86.6 \pm 11.3	0.516
E/A	0.87 \pm 0.13	1.09 \pm 0.04	<0.001**
IVRT (millisec)	68.0 \pm 24.5	28.2 \pm 12.6	<0.001**
DT (millisec)	262.1 \pm 20.7	209.7 \pm 14.9	<0.001**
RFP (millisec)	159.3 \pm 21.5	173.9 \pm 25.6	<0.001**
AFP (millisec)	127.8 \pm 13.5	104.7 \pm 10.7	<0.001**
E/e'	10.6 \pm 1.9	7.34 \pm 0.43	<0.001**

** very significant

The increase in the heart rate is more in the group II when compared to group I after exercise and it is statistically significant. This showed that group I subjects had a lesser peak heart rate than group II subjects. Similarly systolic blood pressure showed a more elevation in group II than group I and diastolic blood pressure showed a more decline in group II subjects inferring that the left ventricular systolic function and left ventricular relaxation are normal in group II subjects.

E velocity showed a significant elevation in group II subjects than group I whereas A velocity in both the groups were similar with no statistical significance.

IVRT showed a marked decline in group II subjects suggesting that the diastolic function is normal. Deceleration time showed an increased duration in group I than group II and was statistically significant.

Rapid filling period is prolonged in group II subjects whereas atrial filling period is decreased after exercise.

Higher filling pressure in group I subjects is implicated by an increased E/e' ratio by more than 10 whereas the group II subjects with normal filling pressure showed a value of around 7.

Table 7 depicts the data obtained in group I subjects after exercise. They are further sub divided into two subgroups depending on the changes in E and A velocity.

The first subgroup comprised of subjects who showed an increase in E/A ratio with exercise and the second subgroup comprised of subjects who showed no change or even a decline in E/A ratio.

As far as heart rate change is concerned, there is no marked difference between the two subgroups. Exercise time is increased in the first subgroup inferring that these subjects had greater effort tolerance. The reason that may be attributed for this significant difference could be that these subjects were showing an increased E/A ratio. The E/A ratio increase in the first group also infer that there is some degree of preservation of diastolic function.

The increase in E velocity is the predominant cause for an increase in E/A ratio in the first subgroup rather than a decline of A velocity.

Table 7 : Effects of exercise on trans-mitral Doppler parameters in subjects with resting Grade I DD (Group I) showing either an E/A decrease or increase with exercise

Doppler variables	E/A increase with exercise Mean \pm SD (n = 34)	E/A decrease with exercise Mean \pm SD (n = 18)	P value
Peak heart rate change (beats /min)	70 \pm 21	73 \pm 24	0.68
Exercise time (min)	9.4 \pm 1.6	7.2 \pm 1.1	<0.001**
E change (cm/sec)	+ 21 \pm 018	-1 \pm 14	0.08
A change (cm/sec)	+11 \pm 18	+6 \pm 20	0.62
E/A change	+0.11 \pm 0.08	-0.05 \pm 0.07	<0.001**
IVRT change (metre sec)	-20 \pm 40	-2 \pm 36	0.133

** very significant

DISCUSSION

In normal persons, with exercise there is an increase in cardiac output. During the initial part, the increase in cardiac output is exercise mediated whereas in the later part the increase in cardiac output is attributed to the increase in heart rate^{11,12}.

In this study, we have come across certain significant correlations related to exercise related diastolic dysfunction in patients with diabetes, hypertension and coronary artery disease¹³⁻¹⁷. This finding has been found in other studies also.

There is a strong correlation between increased E/e' and exercise intolerance. The patients who develop diastolic dysfunction during exercise are those patients who have early exercise intolerance¹⁸⁻²².

The other important point of discussion is atrial compensation. The patients already having diastolic dysfunction at rest are already in a state of atrial compensation. The already compensated atria could not further compensate during exercise and hence these patients have relatively early exercise intolerance.

To the contrary, the subjects with normal resting transmitral pattern have a greater exercise tolerance because during exercise the atrial contribution to left ventricular filling is increased and there is a

shortening of isovolumic relaxation. This finding is also similar to other findings²³.

To emphasize further, exercise tolerance is related to diastolic filling patterns. The abnormal filling pattern is related to early exercise intolerance and normal filling pattern to improved exercise tolerance. Hence subjects with diastolic dysfunction are those subjects who develop early exercise intolerance and those without diastolic dysfunction have good effort tolerance.

Another way of analyzing exercise tolerance is simply to evaluate the exercise time. Shorter the exercise duration means more the exercise intolerance. Dyspnea and fatigue are some common causes for stoppage of exercise which are either due to a decrease in cardiac output and/or an elevated left ventricular filling pressures.

Three important echo parameters that had shown a stronger statistical correlation with exercise intolerance are non shortening of isovolumic relaxation time, shortened deceleration time and continued E/A reversal^{2,13-17,24,25}.

There are previous studies which have demonstrated that there is a further increase in grade of diastolic dysfunction in hypertensive subjects

due to an increase in left ventricular filling pressures which have correlated with natriuretic peptides and E/e'²⁰.

There are some other studies that have shown that a decreased peak annular filling velocity correlated with diastolic dysfunction and E/e' ratio have shown correlation with mean pulmonary capillary pressure.

There are two important inferences from the study. First, the subjects who had pre-existing diastolic dysfunction, and continue to have E/A reversal post exercise have reduced exercise tolerance. At the same time, the subjects who had pre-existing diastolic dysfunction but did not continue to have E/A reversal had a better exercise tolerance. This finding is consistent with other studies²³.

Secondly, the subjects who had normal diastolic function but who developed E/A reversal post exercise also showed reduced exercise tolerance. Other studies²³ have further demonstrated a correlation of E/A reversal not only to reduce exercise tolerance but also with E/e' and brain natriuretic peptides.

LIMITATIONS OF THE STUDY

1. The sample population is small
2. The subjects referred for exercise echocardiography in this study were predominantly low risk group for coronary artery disease.

CLINICAL IMPLICATIONS

E/e' at rest and post exercise is a handy echoparameter to the cause of dyspnea evaluation. Dyspnea is due to an elevated filling pressures in these group of people^{19,20,22}.

At the same time, E/e' is a useful echocardiographic tool irrespective of systolic function. The subjects with reduced or preserved left ventricular function have shown that the persistence of E/e' reversal or the appearance or E/e' reversal post exercise is a strong predictor for exercise intolerance.

The development of ischemia with exercise can also cause dyspnea but the study population did not include such people.

However fatigue is an important symptom which prevented further exercise in many of the subjects. We are not able to ascertain whether elevated left ventricular filling pressures had caused fatigue. Nevertheless, atrial contribution for left ventricular stroke volume can be an important factor. In subjects with diastolic dysfunction atrial contribution is reduced which leads further to a decrease in stroke volume and thereby fatigue and the increase in cardiac output is mainly contributed by increased in heart rates.

CONCLUSION

1. The functional capacity/ exercise tolerance among subjects with grade I diastolic dysfunction at rest showed a heterogenous pattern.
2. The post exercise transmitral Doppler changes among subjects with grade I diastolic dysfunction at rest showed divergent patterns which can aid in evaluating degree of diastolic dysfunction.
3. There is a clear correlation between the functional capacity/exercise tolerance with post exercise transmitral Doppler changes in both groups
4. The appearance of E/A reversal post exercise in people with previous normal transmitral patterns also have exercise intolerance
5. Transmitral Doppler pattern at rest and post exercise gives further thoughts about impaired relaxation of left ventricle

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INFORMATION TO PARTICIPANTS

TITLE:

“EXERCISE TOLERANCE AND POST EXERCISE DIASTOLIC FILLING PATTERN IN PATIENTS WITH RESTING GRADE I DIASTOLIC DYSFUNCTION ”

Principal Investigator:

Co-Investigator (if any):

Name of Participant:

Site: RGGGH& MMC, Chennai

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

We wanted to evaluate regional myocardial function using tissue Doppler imaging before and after PTCA of left anterior descending coronary artery

We have obtained permission from the Institutional Ethics Committee.

The study design

It is a prospective follow up study.

Study Procedures

- In patients with stable angina after myocardial infarction coronary angiogram was done. We select patients with single vessel disease involving left anterior descending coronary artery and study the changes in tissue Doppler imaging findings before and after coronary angioplasty.

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings,

Will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution.

You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator

Signature of Participant

Date

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பெயர் :

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:

பால் :

ஆராய்ச்சி சேர்க்கை எண் :

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது. எனக்கு விளக்கப்பட்ட விவரங்களை புரிந்து கொண்டு நான் எனது சம்மதத்தைத் தெரிவிக்கிறேன்.

எனக்கு இந்த ஆராய்ச்சியில் பங்கேற்க சம்மதம். இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் தான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின் வாங்கலாம் என்பதையும், அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் புரிந்து கொண்டேன். இந்த ஆராய்ச்சியின் விவரங்களைக் கொண்ட தகவல் தாளப் பெற்றுக் கொண்டேன்.

இந்த ஆராய்ச்சியின் விவரங்களையும் அதன் நோக்கங்களை யும் முழுமையாக புரிந்து கொண்டு எனது சுயநினைவுடன் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதிக்கிறேன்.

கையொப்பம்

ABBREVIATIONS

DD	-	Diastolic Dysfunction
LVH	-	Left Ventricle Hypertrophy
LV	-	Left Ventricle
MRI	-	Magnetic Resonance Imaging
CAD	-	Coronary Artery Disease
DT	-	Deceleration Time
IVRT	-	Isovolumic Relaxation Time
DFP	-	Diastolic Filling Period
E	-	Peak Rapid Filling Velocity
A	-	Peak Atrial Filling Velocity
LVEDV	-	Left Ventricular End Diastolic Volume
LVESV	-	Left Ventricular End Systolic Volume
LVEDD	-	Left Ventricular End Diastolic Diameter
LVESD	-	Left Ventricular End Systolic Diameter
DM	-	Diabetes Mellitus
SHT	-	Systemic Hypertension
SBP	-	Systolic Blood Pressure
DBP	-	Diastolic Blood Pressure
ECG	-	Electrocardiogram
HR	-	Heart Rate

PROFORMA FOR PATIENT'S DATA COLLECTION

STUDY TITLE:

“EXERCISE TOLERANCE AND POST EXERCISE DIASTOLIC FILLING PATTERN IN PATIENTS WITH RESTING GRADE I DIASTOLIC DYSFUNCTION ”

Name	Age	Sex	Address
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Symptoms

Cardiac symptoms if any

h/OHypertension h/O Diabetes mellitus

Family history

Signs

HR	SBP	DBP
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S1

A2 P2

Murmurs

ECG

TRANSTHORACIC ECHOCARDIOGRAM(AT REST)

LVEDV LVEDV LVEF E velocity A velocity IVRT DT

RFP AFP E/e'

TMT PARAMETERS

Peak HR Peak SBP Peak DBP Exercise Time

TRANSTHORACIC ECHOCARDIOGRAM (POST EXERCISE)

LVEDV LVEDV LVEF E velocity A velocity IVRT DT

RFP AFP E/e'

IMAGE I

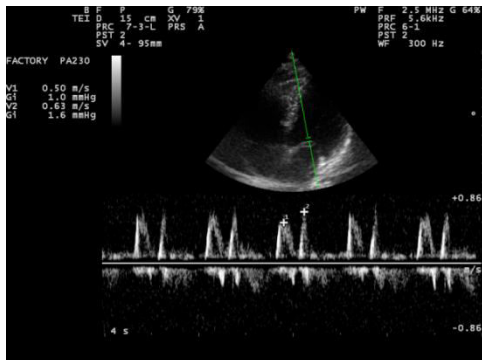


IMAGE II

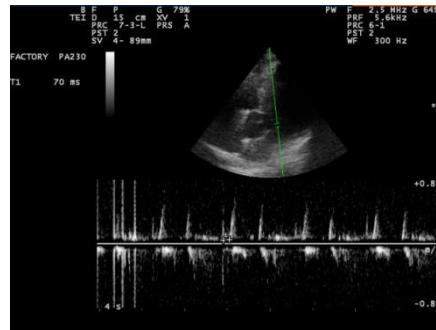


IMAGE III

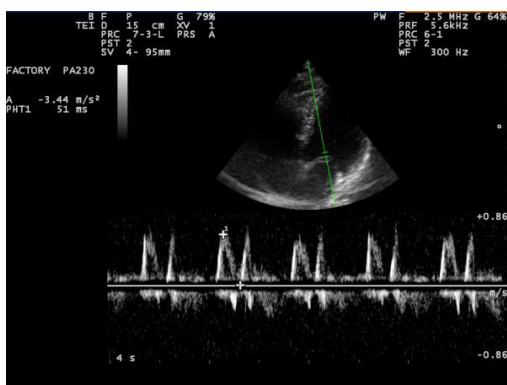


IMAGE IV

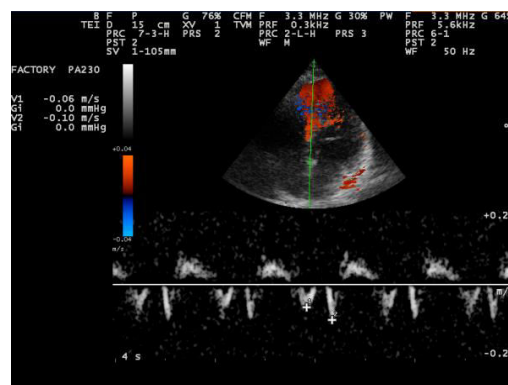


Fig.1 showing mean values of Heart rate, SBP and DBP at rest
in Group I subjects

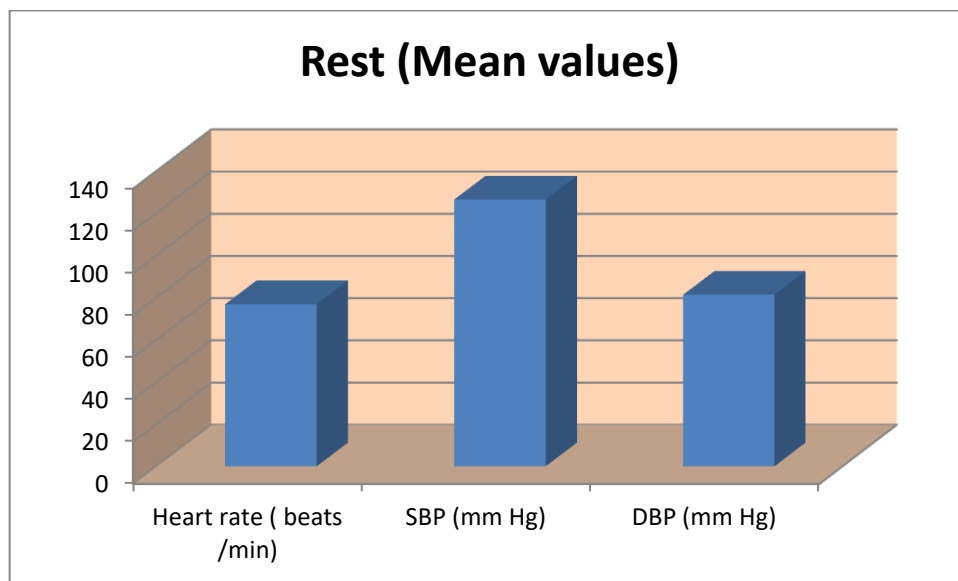


Fig.2 showing mean values of Heart rate, SBP and DBP at exercise
in Group I subjects

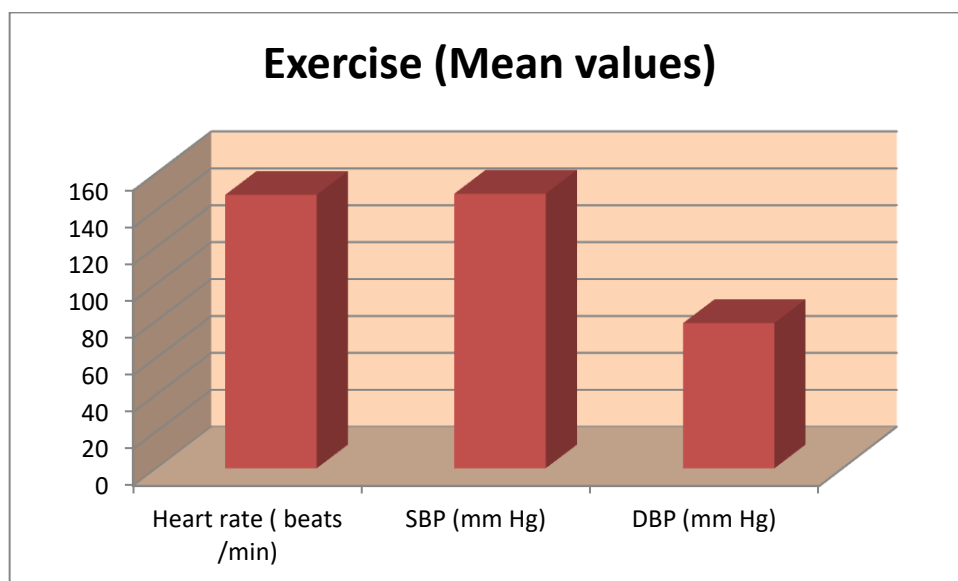


Fig.3 showing mean values of E velocity, A velocity ,E/A at rest
in Group I subjects

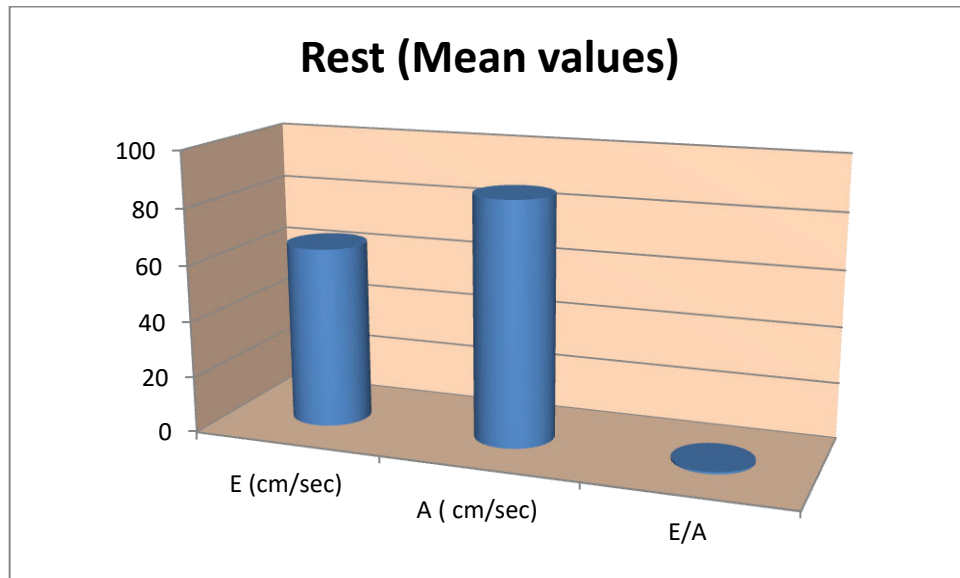


Fig.4 showing mean values of E velocity, A velocity, E/A at rest
in Group I subjects

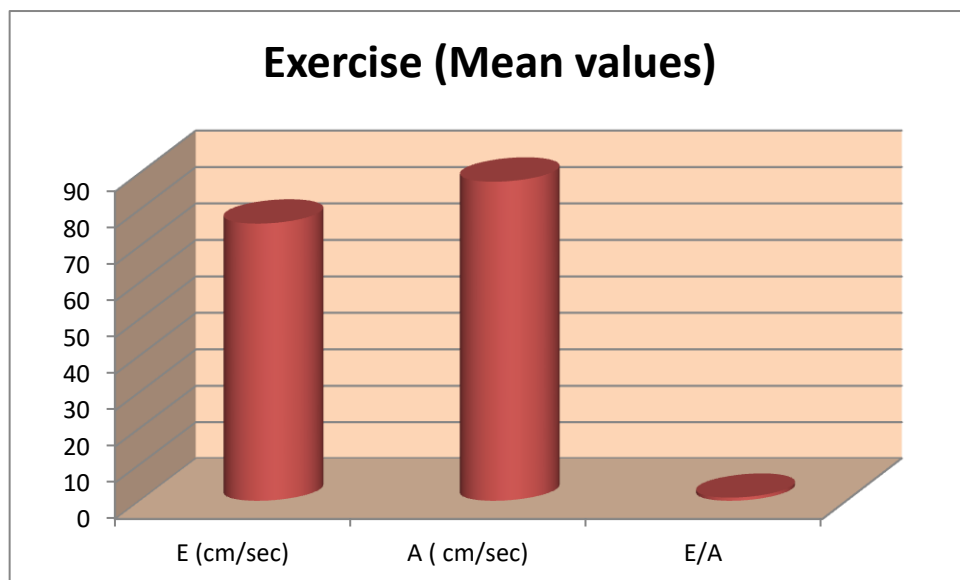


Fig.5 showing mean values of IVRT, DT and E/e' at rest
in Group I subjects

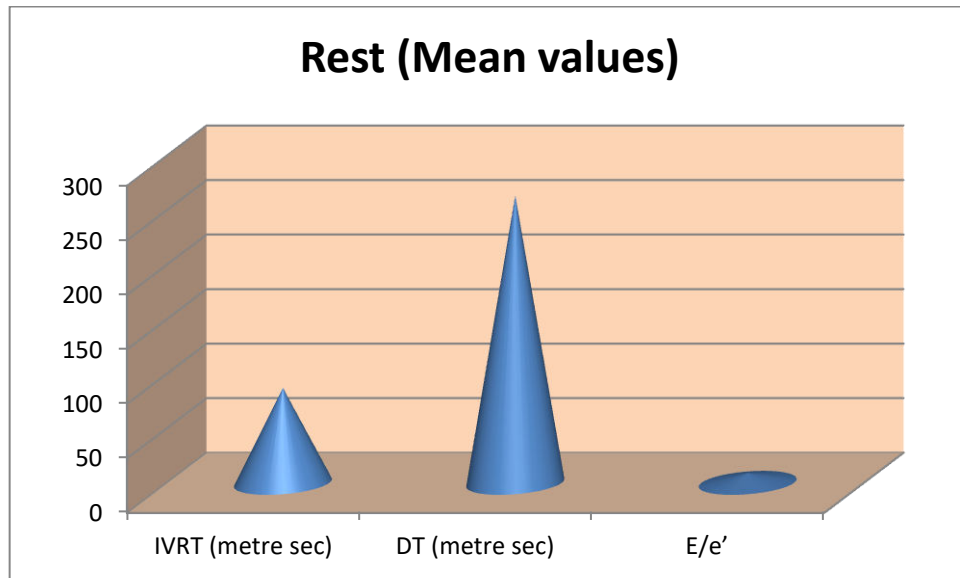
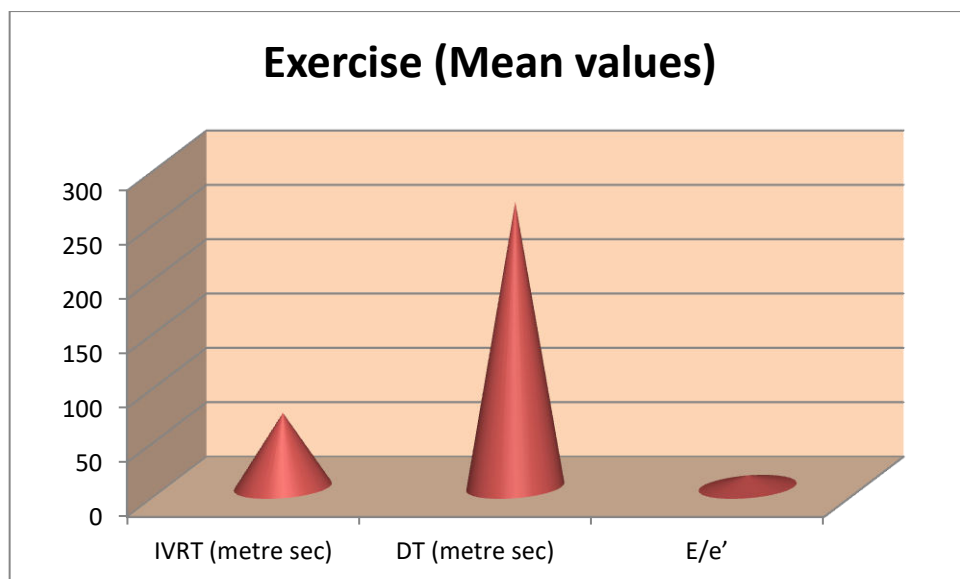


Fig.6 showing mean values of IVRT,DT and E/e' at exercise
in Group I subjects



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